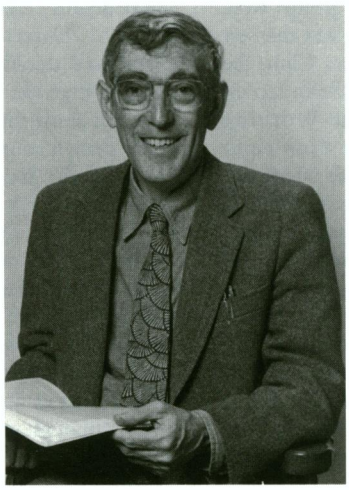
DNA by the Bay

Across the bay from the Golden Gate Bridge, one of the first NIEHS Environmental Health Sciences Centers (EHSC) was established in 1978. Here, at the University of California at Berkeley, a modern day gold rush continues as world-class researchers unearth scientific riches.

The University of California Environmental Health Sciences Center

The EHSC at the University of California at Berkeley brings together 16 scientists from the departments of molecular and cell biology, statistics, and nutrition; the College of Natural Resources; and the School of Public Health, all of whom have a strong interest in the area of DNA damage and its consequences for environmental health, and in understanding the causes, mechanisms, and prevention of this damage.



G. Paul Bishop

Bruce N. Ames

"Our center is a little more basic research oriented than some," says Bruce N. Ames, a professor of biochemistry and molecular biology and director of the center since its inception. He is assisted by Deputy Director Stuart Linn, a world leader in DNA repair. The center began with molecular biologists focusing on DNA. About a decade ago, the scope was broadened to include scientists with a range of public health expertise, a trend that continues. "But we've always kept a strong basic research effort in DNA damage and mutagenesis," Ames says.

The center can be thought of as combining three levels of attack on environmental health problems: examination of potential human cancer risks via animal and *in vitro* tests, studies of human populations, and elucidation of molecular mechanisms. The center's scientists unanimously praise the multidisciplinary nature of the center and the synergistic collaborations that have resulted, saying it encourages research they wouldn't be able to consider otherwise. "It's been a catalyst for bringing us together," says Allan Smith, a professor of epidemiology. Smith also appreciates the small, peer-reviewed mini-grants that fund preliminary research projects. "The seed funding part of the program has been outstanding," he says.

Organization

The center is organized into six research cores, six facility cores, two service cores, an administrative core, and a community outreach and education core. The research cores are the heart of the center. The mutagenesis and carcinogenesis research core is concerned with identifying the mechanisms of mutation, identifying significant mutagens, understanding the consequences for cancer, and developing preventive strategies. Scientists working in the DNA repair, replication, and recombination core explore how chemicals damage DNA, how such damage is repaired, and how mutagenesis and mechanisms of DNA replication are related. The human genetics–environment interactions core focuses on the interaction between human genetic variability and environmental factors. The goal of the germline mutation–teratogenesis core is to identify significant germline mutagens and determine how lack of essential nutrients affects the germline or developing fetus. Members of the virology and chronic infection core seek to understand how inflammation due to chronic infection causes cancer. The nutrition–environment interactions core supports and promotes research on the role of nutritional factors in protecting the genome and modifying effects of environmental factors.

Facility cores provide specialized instrumentation, capabilities, and services that support numerous research efforts. A variety of sophisticated equipment makes the analytical facility key for various molecular investigations. For instance, Ames' group used an extremely sensitive gas chromatograph–mass spectrometer assay to reveal how folate deficiency leads to chromosome breakage due to increased incorporation of uracil into DNA. The other facility cores include computer resources, DNA synthesis and sequencing, electron microscope, tissue culture and media, and monoclonal antibody.

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Lois Gold

Worldwide Resources

The two service cores—the *Salmonella* mutagenicity test resource and the carcinogenic potency database—are truly worldwide resources that have been part of the center since it was formed. Ames began developing the *Salmonella*/liver test for mutagenicity, widely known as the Ames test, before the center existed, but the center has played an important role in supporting improvements and making the tester strains available. The test is a rapid, cost-effective way to test chemicals for their ability to react with DNA and is in use in more than 3,000 government, academic, and industrial labs around world.

Recently, Ames' lab considerably improved the *Salmonella* tester strains, engineering them so they are diagnostic for the type of mutation caused by a specific mutagen; each of the six strains implicates a particular base pair substitution. The new strains are also more sensitive and have a lower spontaneous mutation rate.

The carcinogenic potency database (CPDB) standardizes and consolidates into a single resource the world's diverse literature on chronic, long-term animal cancer tests. This definitive database includes both qualitative and quantitative information on positive and negative tests from more than 1,000 papers published in the scientific literature, as well as 400 technical reports from the National Toxicology Program/National Cancer Institute bioassay program. Results for 5,152 experiments on 1,298 chemicals have been examined and analyzed and an index of carcinogenic potency computed. "It's a gold mine as a reference source. There's nothing like it," says Lois Gold, senior scientist at Lawrence Berkeley Laboratory and director of the CPDB project for 16 years.

This resource is readily available to the world's researchers. The database has been published in six different *EHP* volumes to date and the whole database will soon be published in a handbook. The CPDB is also available electronically, and more than 100 organizations have requested the whole database. Much of the data is accessible via the CPDB World Wide Web site. "Our Web site has gotten remarkable response," Gold says. Some 7,500 individual computers in 60 countries had accessed the site before its first anniversary earlier this year.

Gold, Ames, and other center members have made good use of the CPDB them-

selves, examining problems of extrapolation between species and comparing natural and synthetic chemicals, and relative risks. Half the chemicals in the CPDB, whether natural or synthetic, test positive for carcinogenicity. This high positivity rate seems to be due to the high doses used in bioassays. Even though about 80% of the chemicals tested are synthetic, more than 99% of the chemicals most people are exposed to are natural. "So we've ranked them on an index comparing the human exposure to the dose that gave rodents tumors," Gold says. They've also created other rankings, such as for chemicals as carcinogenic hazards in the workplace. With the CPDB, the researchers have broadened the perspective on the interpretation and use of bioassay results to estimate human risk and raised questions about the causes of cancer.

Dietary Connections

"One major aspect of our center has been to understand what really is damaging DNA and how to prevent it. It's becoming very clear you need a good diet for keeping your chromosomes together," says Ames, who continues to be a major leader in the area of oxidative damage to DNA, combining issues of cancer, diet, and aging.

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Gladys Block

Center member Gladys Block, a professor of public health nutrition, recently reviewed more than 150 epidemiological studies on diet and cancer. The results, which were overwhelmingly consistent, indicated that the quarter of the population eating the fewest fruits and vegetables had double the incidence rate for most cancers compared to the quarter eating the most fruits and vegetables. Other than stopping smoking, the biggest effects in lowering the cancer rate are going to come from improved nutrition, Ames says. "That's where the gold is in terms of health and prevention."

Studies at the center indicate that a sizable proportion of poor people are deficient in various micronutrients that are involved in protecting DNA against damage, such as folate and vitamin C. Ames' lab has shown that men with low vitamin C intake have a fourfold lower level of the vitamin in their seminal fluid and a 2.5-fold increase in oxidative damage in their sperm DNA. "If you don't put oil in your car, it doesn't last very long. And if you don't get your micronutrients . . . then you're in trouble because it fouls up your biochemistry. We have real work to do," Ames says, "and that's to get people on good diets."

Teamwork and Population Studies

Arsenic has long been known to cause lung and skin cancer, depending on the route of exposure. Smith's work suggests that arsenic exposure is a major factor in bladder cancer as well. Where arsenic is abundant in the earth's crust, it leaches into the water. Smith has studied small populations in California and Nevada, and larger populations in countries such as Argentina and Chile, where people are exposed to higher levels. His studies in Argentina show death rates from bladder and lung cancer were higher in populations exposed to high levels of arsenic.

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Stuart Linn

In another exposed population in Chile, traditional epidemiological methods were combined with novel laboratory techniques developed by Martyn Smith, a professor of toxicology and also a center member. Biomarker techniques permit researchers to quickly obtain molecular and chromosomal data in briefer studies of fewer people. The noninvasive, *in vitro* test examines exfoliated cells collected from urine. "What we show is that there's genetic damage in people [exposed to arsenic] at or around the American drinking water standard, which is somewhat disturbing," says Smith, who is also director of the NIEHS Superfund Basic Research Program.

Martyn Smith focuses on developing biomarkers of susceptibility and early effect and applying them to the study of human populations exposed to various chemicals. The techniques employed include fluorescence *in situ* hybridization to detect chromosome damage and PCR to detect genetic susceptibility. He has also applied biomarker research to studying people exposed to solvents such as benzene, which is known to cause leukemia. In a study of exposed workers in China, Smith's work showed that benzene produces selective chromosome damage, aberrations specifically related to leukemia development, and that these can be detected in otherwise healthy workers.

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Martyn Smith

Looking Ahead

With the premise in mind that if the environment can be made safe for children (arguably our most vulnerable population), then it is likely to be safe for everyone, Martyn Smith has proposed a Center for Children and the Environment. Such a center is an exciting possibility that may take shape within the next several years.

The current center's emphasis on nutrition is expected to continue and increase. "We're all suddenly aware now that nutrition is an underdeveloped field. We don't know as much as we think we know," says Linn.

Plans to improve outreach include expanding the center's Web site. In addition to the CPDB, the site includes numerous full text publications and a variety of links to member scientists' homepages and related sites. Several members of the center also contribute regularly to the *Berkeley Wellness Letter*, one of the country's most successful health newsletters, reaching nearly a million subscribers with its information on health-related discoveries.

Ames and others argue that the current practice by many research institutions of investing resources in, for example, chasing after a part per billion of synthetic carcinogens in water, is counterproductive. If the goal is saving the most lives per dollar spent, the focus should be on the largest populations at the highest risk, they maintain. Center scientists will continue to be instrumental in identifying both the populations and the risk.

Carolyn J. Strange